PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JAB1703f-PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/03240	International filing date *(day/month/year)* 26.03.2003	Priority date *(day/month/year)* 29.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K51/04		
Applicant JANSSEN PHARMACEUTICA N.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04.09.2003	12.07.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Dullaart, A Telephone No. +31 70 340-3290

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/03240

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-127 as originally filed

Claims, Numbers

1-20 as originally filed

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form:

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-6 AND 8-20 IN PART

   because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☒ the claims, or said claims Nos. 1-6 AND 8-20 IN PART are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-6 AND 8-20 IN PART

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

During the search stage, the following objection was raised under Article 6 PCT.
Present claims 1-6 and 8-10 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds tested in table 10, and to those compounds mentioned specifically in claim 7.
The International Preliminary Examination Authority fully agrees with these objections, and will limit the International Preliminary Examination accordingly.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Patent Abstracts of Japan, vol. 2000, no. 09, 13 October 2000 (2000-10-13) & JP 2000 169450 A (KYORIN PHARMACEUT CO LTD), 20 June 2000 (2000-06-20)

D2: WO 99 26927 A (STORMANN THOMAS M ;DELMAR ERIC G (US); MOE SCOTT T (US); SMITH DAR) 3 June 1999 (1999-06-03)

**D3: STONE T W: 'Development and therapeutic potential of kynurenic acid and kynurenine derivatives for neuroprotection'
Trends in Pharmacological Sciences, Elsevier Trends Journal, Cambridge, GB, vol. 21, no. 4, April 2000, pages 149-154, XP004196017 ISSN: 0165-6147**

**D4: SING-YUEN S et al.: '3-Hydroxy-quinolin-2-ones: inhibitors of [H]-glycine binding to the site associated with the NMDA receptor'
Bioorganic & Medicinal Chemistry Letters, Oxford, GB, vol. 6, no. 5, 5 March 1996 (1996-03-05), pages 499-504, XP004135016 ISSN: 0960-894X**

D5: WO 99 03822 A (KOZIKOWSKI ALAN P ;UNIV GEORGETOWN (US); ARALDI

GIAN LUCA (US); ST) 28 January 1999 (1999-01-28)

D6: WO 94 27605 A (OREGON STATE ;UNIV CALIFORNIA (US)) 8 December 1994 (1994-12-08)

D7: MUTEL Vincent et al.: 'Characterization of (3H)quisqualate binding to recombinant rat metabotropic glutamate 1a and 5a receptors and to rat and human brain sections.'
Journal of Neurochemistry, vol. 75, no. 6, December 2000 (2000-12), pages 2590-2601, XP002226239 ISSN: 0022-3042

D8: PENG C T et al.: 'An Evaluation of Different Methods for Tritium Labelling'
Fusion Technology, American Nuclear Society, Lagrange Park, Illinois, US, vol. 21, no. 2 PT 2, 1 March 1992 (1992-03-01), pages 307-311, XP000271846 ISSN: 0748-1896

D9: BRUNDISH et al.: 'Tritium labeling by selective debromination'
Journal of Labelled Compounds and Radiopharmaceuticals, Sussex, GB, vol. 25, no. 12, 1988, pages 1361-1369, XP002079113 ISSN: 0362-4803

D1 describes similar compounds having an affinity for similar receptors.
D2 and **D3** disclose similar compounds having similar activity.
D4 teaches that 3-hydroxy-quinolin-2-ones are inhibitors of [H]-glycine binding to the site associated with the NMDA receptor
D5 describes different compounds for marking the same receptors
D6 discloses similar radiolabelled compounds, having an affinity for glycine-sites. The procedure for determining the affinity of a compound for the mGlu1 receptor is described in **D7**.
Finally, general techniques pour radiolabelling a compound with tritium are described in **D8** and **D9**.

In claim 7, specific radiolabelled compounds are claimed, which have not been described in the prior art. The problem to be solved by these compounds is the provision of further compounds for marking or identifying a mGlu1 receptor in biological material. The closest prior art is given in **D5**, which describes different compounds for the same use. The presently claimed compounds can be distinguished from this prior art by their structure.

In support of the claimed activity, the applicant has provided an *in vitro* test. In this test, the competitive affinity of glutamate and ^{3}H-quisqualate is compared to the competitive

affinity of ^{3}H-compound A and some other labelled compound with affinity for the mGlu1 receptor. Unfortunately, there is no data on file which explains, why the results of the experiments can be extrapolated to such a large Markush-type formula. The Examining Division therefore has severe doubts as to whether the problem underlying the present application is actually solved by all solutions as claimed.

Furthermore, since the affinity of compound A is compared to the affinity of compound 135 (see page 110, lines 7-27) it is not clear, which of the compounds as described in the present application actually are intended to fall within the claimed scope of protection. Indeed, table 10 seems to list a preferred group of compounds within the scope of present claim 1, containing both compound 135 and compound 432 (being the unlabelled version of compound A). Yet, compound A is compared to compound 135 as if the latter were part of the prior art. Due to this clear contradiction, only claim 7 seems to list specific compounds, for which patent protection is apparently sought. For these compounds, however, it is still necessary to demonstrate, that the problem underlying the present application has indeed been solved, with the exception of compound A.

In this context it is further to be noted, that the labelling of a test compound is the most standard labelling used. Documents **D8** and **D9** have been cited to demonstrate this. Thus, the mere labelling of a compound using tritium is on itself not sufficient to establish an inventive step in the sense of Article 33.3 PCT.